Complete Summary

GUIDELINE TITLE

Expert consensus document on the use of antiplatelet agents. The task force on the use of antiplatelet agents in patients with atherosclerotic cardiovascular disease of the European Society of Cardiology.

BIBLIOGRAPHIC SOURCE(S)

Patrono C, Bachmann F, Baigent C, Bode C, De Caterina R, Charbonnier B, Fitzgerald D, Hirsh J, Husted S, Kvasnicka J, Montalescot G, Garcia Rodriguez LA, Verheugt F, Vermylen J, Wallentin L, Priori SG, Alonso Garcia MA, Blanc JJ, Budaj A, et al. Expert consensus document on the use of antiplatelet agents. The Task Force on the Use of Antiplatelet Agents in Patients with Atherosclerotic Cardiovascular Disease of the European Society of Cardiology. Eur Heart J 2004 Jan;25(2):166-81. [75 references] PubMed

GUIDELINE STATUS

This is the current release of the guideline.

** REGULATORY ALERT **

FDA WARNING/REGULATORY ALERT

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory information has been released.

On September 30, 2004, Vioxx (rofecoxib) was withdrawn from the U.S. and worldwide market due to safety concerns of an increased risk of cardiovascular events. See the U.S. Food and Drug Administration (FDA) Web site for more information.

Subsequently, on April 7, 2005, after concluding that the overall risk versus benefit profile is unfavorable, the FDA requested that Pfizer, Inc voluntarily withdraw Bextra (valdecoxib) from the market. The FDA also asked manufacturers of all marketed prescription nonsteroidal anti-inflammatory drugs (NSAIDs), including Celebrex (celecoxib), a COX-2 selective NSAID, to revise the labeling (package insert) for their products to include a boxed warning and a Medication Guide. Finally, FDA asked manufacturers of non-prescription (over the counter [OTC]) NSAIDs to revise their labeling to include more specific information about the potential gastrointestinal (GI) and cardiovascular (CV) risks, and information to assist consumers in the safe use of the drug. See the FDA Web site for more information.

Most recently, on June 15, 2005, the FDA requested that sponsors of all non-steroidal anti-inflammatory drugs (NSAID) make labeling changes to their products. FDA recommended proposed labeling for both the prescription and over-the-counter (OTC) NSAIDs and a medication guide for the entire class of prescription products. All sponsors of marketed prescription NSAIDs, including Celebrex (celecoxib), a COX-2 selective NSAID, have been asked to revise the labeling (package insert) for their products to include a boxed warning, highlighting the potential for increased risk of cardiovascular (CV) events and the well described, serious, potential life-threatening gastrointestinal (GI) bleeding associated with their use. FDA regulation 21CFR 208 requires a Medication Guide to be provided with each prescription that is dispensed for products that FDA determines pose a serious and significant public health concern. See the FDA Web siteFDA Web site for more information.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Atherosclerotic cardiovascular disease

GUIDELINE CATEGORY

Management
Prevention
Treatment

CLINICAL SPECIALTY

Cardiology
Family Practice
Internal Medicine

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

- To integrate a mechanistic understanding as to why some antiplatelet drugs work and some do not, with an evidence-based definition of categories of patients for whom the benefits of antiplatelet therapy clearly outweigh the risk of bleeding complications
- To provide the practising cardiologist with a novel instrument to guide his/her choice of the most suitable antiplatelet strategy for the individual patient with different clinical manifestations of ischaemic heart disease

TARGET POPULATION

Patients with atherosclerotic cardiovascular disease including patients with a history of myocardial infarction, stroke, transient ischaemic attack, stable angina, peripheral arterial disease, and atrial fibrillation

INTERVENTIONS AND PRACTICES CONSIDERED

1. Aspirin
2. Ticlopidine
3. Clopidogrel
4. Dipyridamole
5. Abciximab
6. Eptifibatide
7. Tirofiban
8. Indobufen
9. Triflusal
10. Picotamide

MAJOR OUTCOMES CONSIDERED

- Cardiovascular morbidity and mortality
- Combined outcome of nonfatal myocardial infarction, nonfatal stroke, and vascular death
- Risk of a serious vascular event
- Risk of major bleeding complications

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Not stated

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Strength of Evidence

A. Data derived from at least two randomized clinical trials or meta-analyses
B. Data derived from a single randomized trial and/or meta-analysis from nonrandomized studies
C. Consensus opinion of the experts based on trials and clinical experience

METHODS USED TO ANALYZE THE EVIDENCE

Review of Published Meta-Analyses
Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Not stated

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Usefulness or Efficacy of a Recommended Treatment

Class I: Evidence and/or general agreement that a given treatment is beneficial, useful, and effective

Class II: Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment

Class IIa: Weight of evidence or opinion is in favour of usefulness/efficacy

Class IIb: Usefulness/efficacy is less well established by evidence/opinion.

Class III: Evidence or general agreement that the treatment is not useful/effective and in some cases may be harmful.

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Not stated

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Recommendations concerning individual antiplatelet agents

Aspirin

- Aspirin once daily is recommended in all clinical conditions in which antiplatelet prophylaxis has a favourable benefit/risk profile.
- Because of gastrointestinal (GI) toxicity and its potential impact on compliance, physicians are encouraged to use the lowest dose of aspirin that was shown to be effective in each clinical setting.
- The available evidence supports daily doses of aspirin in the range of 75 to 100 mg for the long-term prevention of serious vascular events in high-risk patients (i.e., $\geq$3% per annum).
- In clinical situations where an immediate antithrombotic effect is required (such as in acute coronary syndromes or in acute ischaemic stroke), a loading dose of 160 to 300 mg should be given at diagnosis in order to ensure rapid and complete inhibition of thromboxane (TX)-A2-dependent platelet aggregation.
- No test of platelet function is recommended to assess the antiplatelet effect of aspirin in the individual patient.
- The routine use of proton pump inhibitors or cytoprotective agents is not recommended in patients taking daily doses of aspirin in the range of 75 to 100 mg, because of lack of randomized trials demonstrating the efficacy of such protective strategies in this setting.
- Nonsteroidal anti-inflammatory drugs (NSAIDs) have been investigated inadequately in terms of their potential cardiovascular effects. Thus, physicians prescribing these drugs to arthritic patients with prior vascular complications should not discontinue treatment with low-dose aspirin.
- Because of potential pharmacodynamic interactions between traditional NSAIDs (e.g., ibuprofen) and aspirin, patients treated with low-dose aspirin requiring NSAID therapy may benefit from the use of selective cyclooxygenase-2 (COX-2) inhibitors.

Ticlopidine

- The role of ticlopidine in the present therapeutic armamentarium is uncertain. Now that ticlopidine is available as a generic drug in many countries, its lower

cost as compared to clopidogrel is being emphasized within a broad cost-containment strategy.
- Although there are no large head-to-head comparisons between the two thienopyridines, indirect comparisons are highly suggestive of a lower burden of serious bone-marrow toxicity with clopidogrel as compared to ticlopidine.
- In contrast to clopidogrel, ticlopidine does not have an approved indication for patients with a recent myocardial infarction.

Clopidogrel

- Although clopidogrel may be slightly more effective than aspirin, the size of any additional benefit is statistically uncertain and the drug has not been granted a claim of superiority versus aspirin by regulatory authorities.
- Clopidogrel, 75 mg daily, is an appropriate alternative for high-risk patients with coronary, cerebrovascular or peripheral arterial disease who have a contraindication to low-dose aspirin.
- The results of the Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) trial have led to FDA approval of a new indication for clopidogrel in patients with acute coronary syndromes without ST-segment elevation. A loading dose of 300 mg clopidogrel should be used in this setting followed by 75 mg daily. Revision of the existing guidelines will need a consensus agreement by the experts with respect to timing of percutaneous coronary intervention, length of clopidogrel treatment, and combination with glycoprotein (GP) IIb/IIIa antagonists.

Dipyridamole

- Although the combination of low-dose aspirin and extended-release dipyridamole (200 mg twice a day) is considered an acceptable option for initial therapy of patients with non-cardioembolic cerebral ischaemic events, there is no basis to recommend this combination in patients with ischaemic heart disease.

Abciximab, eptifibatide and tirofiban

- The benefit/risk profile of currently available GPIIb/ IIIa antagonists is substantially uncertain for patients with acute coronary syndromes who are not routinely scheduled for early revascularization.
- In contrast, for patients undergoing percutaneous coronary intervention, intensification of antiplatelet therapy by adding an intravenous GPIIb/IIIa blocker is an appropriate strategy to reduce the risk of procedure-related thrombotic complications.

Other antiplatelet drugs

- Indobufen, triflusal, and picotamide are commercially available in a few European countries, based on relatively limited evidence for efficacy and safety.
- Because of substantial statistical uncertainty surrounding the direct randomized comparisons of these antiplatelet agents versus aspirin and inadequate statistical power of the studies to assess reliably any difference in

serious vascular events, the use of indobufen, triflusal, or picotamide instead of aspirin is not recommended.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is not specifically stated for each recommendation.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Balance of Benefits and Risks of Antiplatelet Therapy

- The absolute benefits of aspirin therapy substantially outweigh the absolute risks of major bleeding [particularly, gastrointestinal (GI)] complications in a variety of clinical settings characterized by moderate to high risk of occlusive vascular events. However, in low-risk individuals the benefit/risk profile of such a preventive strategy is uncertain.
- A meta-analysis of four primary prevention trials suggests that aspirin treatment is safe and worthwhile at coronary event risk equal to or greater than 1.5% per year.

Subgroups Most Likely to Benefit

- Allocation of high-risk patients to a prolonged course of antiplatelet therapy reduced the combined outcome of nonfatal myocardial infarction, nonfatal stroke, or vascular death ('serious vascular events') by about 25%.
- Absolute reductions in the risk of having a serious vascular event were 36 per 1,000 treated for 2 years, among patients with previous myocardial infarction; 38 per 1,000 patients treated for 1 month among patients with acute myocardial infarction; 36 per 1,000 treated for 2 years among those with previous stroke or transient ischaemic attack (TIA); 9 per 1,000 treated for 1 month among those with acute ischaemic stroke; and 22 per 1,000 treated for 2 years among other high-risk patients, including those with stable angina, peripheral arterial disease and atrial fibrillation.
- In each of these high-risk categories, the absolute benefits substantially outweighed the absolute risks of major bleeding complications.

Note: Refer to the original guideline document for a discussion of the clinical trial evidence in patients with ischaemic heart disease.

POTENTIAL HARMS

Aspirin therapy is associated with absolute risks of major bleeding [particularly, gastrointestinal (GI)] complications.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

IMPLEMENTATION TOOLS

Personal Digital Assistant (PDA) Downloads
Pocket Guide/Reference Cards

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness
Staying Healthy

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

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ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2004 Jan

GUIDELINE DEVELOPER(S)

European Society of Cardiology - Medical Specialty Society

SOURCE(S) OF FUNDING

European Society of Cardiology Committee for Practice Guidelines

GUIDELINE COMMITTEE

Task Force on the Use of Antiplatelet Agents in Patients with Atherosclerotic Cardiovascular Disease of the European Society of Cardiology

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

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Armenian Society of Cardiology - Medical Specialty Society
Association of Cardiologists of Bosnia & Herzegovina - Medical Specialty Society
Austrian Cardiologists Association - Medical Specialty Society
Belgian Society of Cardiology - Medical Specialty Society
Cardiology Society of Serbia and Montenegro - Medical Specialty Society
Croatian Cardiac Society - Medical Specialty Society
Cyprus Society of Cardiology - Medical Specialty Society
Czech Society of Cardiology - Medical Specialty Society

Estonian Society of Cardiology - Medical Specialty Society
Finnish Cardiac Society - Medical Specialty Society
French Society of Cardiology - Medical Specialty Society
German Society of Cardiology - Medical Specialty Society
Hellenic Cardiological Society - Medical Specialty Society
Hungarian Society of Cardiology - Medical Specialty Society
Israel Heart Society - Medical Specialty Society
Latvian Society of Cardiology - Medical Specialty Society
Lithuanian Society of Cardiology - Medical Specialty Society
Netherlands Society of Cardiology - Medical Specialty Society
Polish Cardiac Society - Medical Specialty Society
Portuguese Society of Cardiology - Medical Specialty Society
Romanian Society of Cardiology - Medical Specialty Society
San Marino Society of Cardiology - Medical Specialty Society
Swiss Society of Cardiology - Medical Specialty Society
Tunisian Society of Cardiology - Medical Specialty Society
Ukrainian Society of Cardiology - Medical Specialty Society

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: Available from the European Society of Cardiology (ESC) Web site.

Print copies: Available from Elsevier Publishers Ltd., 32 Jamestown Road, London, NW1 7BY, United Kingdom. Tel: +44.207.424.4422; Fax: +44 207 424 4433; E-mail: gr.davies@elsevier.com

AVAILABILITY OF COMPANION DOCUMENTS

The following is available:

- Antiplatelet agents. Pocket guidelines. Order form available in Portable Document Format (PDF) from the ESC Web site. Also available for PDA download from the ESC Web site.

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI on May 13, 2004. The information was verified by the guideline developer on July 29, 2004. This summary was updated by ECRI on January 12, 2005 following the release of a public health advisory from the U.S. Food and Drug Administration regarding the use of some non-steroidal anti-inflammatory drug products. This summary was updated on April 15, 2005 following the withdrawal of Bextra (valdecoxib) from the market and the

release of heightened warnings for Celebrex (celecoxib) and other nonselective nonsteroidal anti-inflammatory drugs (NSAIDs). This summary was updated by ECRI on June 16, 2005, following the U.S. Food and Drug Administration advisory on COX-2 selective and non-selective non-steroidal anti-inflammatory drugs (NSAIDs).

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